Attorney's Docket No.: 14174-104US5/RIB001.3USD4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kreutzer & Limmer
Serial No. : 10/612,179
Filed : July 2, 2003
Title : METHOD AND MEDICAMENT FOR INHIBITING THE EXPRESSION OF A DEFINED GENE

Art Unit : 1635
Examiner : Tracy Ann Vivlemore

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Appellants are appealing the final rejection of claims 4-9 in the Final Office Action dated July 13, 2005, and the Advisory Action dated October 19, 2005. A Notice of Appeal is being filed along with this Brief On Appeal.

(i) Real Party in Interest

The real party in interest is Alnylam Europe AG., having a place of business Fritz-Hornschuch-Str. 9, Kulmbach, Fed. Rep. Germany, which is a wholly owned subsidiary of Alnylam Pharmaceuticals Inc., having a place of business at 300 3rd Street, Cambridge, Massachusetts, 02142.

(ii) Related Appeals and Interferences

There are no prior or pending appeals, interferences, or judicial proceedings related to the present application.

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(iii) Status of Claims

Claims 4-9 are pending.

Claims 4-9 are rejected.

Claims 4-9 are being appealed.

(iv) Status of Amendments

All of the amendments in this case have been entered.

(v) Summary of Claimed Subject Matter

The present invention relates to isolated double stranded oligoribnucleotides (dsRNA) for use in inhibiting the expression of a target gene. Specifically, independent claim 4 is drawn to an isolated dsRNA for where the dsRNA consists of two separated non-linked complementary strands between 15 and 21 nucleotides in length which are capable of specifically inhibiting the expression of a mammalian target gene.

(vi) Grounds of Rejection

Claims 4-9 are objected to under 35 USC § 132(a) and stand rejected under 35 U.S.C. § 112, as failing to comply with the written description: a new matter rejection.

Claims 4-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fosnaugh (US 2003/0143732).

(vii) Argument

I. Grouping Of Claims

All of the claims stand rejected under 35 U.S.C. § 112 and 35 U.S.C. § 102(b). Applicants have not addressed the patentability or the application of these rejections to each individual claims. Therefore, for purposes of this appeal, applicants would agree, that as to each rejection, the claims stand or fall together.

II. Basis Of The Rejections Raised

The seminal basis of all of the rejections raised by the Examiner is that the presently pending claims are not entitled to claim priority to PCT application PCT/DE00/00244, filed January 29, 2000, or the US National Phase of this case, US 09/889,802, because the limitations that the isolated oligoribonucleotide "consists of two separate non-linked complementary oligoribonucleotide strands . . . 15-21 nucleotides in length" are not supported by the application as filed.

The Examiner has stated that the priority date for these limitations is July 2, 2003. In view of this priority date, the Examiner has cited art which anticipates the claimed inventions: the cited art having a date of publication after the January 29, 2000 priority claimed by Applicants for these limitations.

Applicants position is that the limitations that the "isolated oligoribonucleotide consists of two separate non-linked complementary oligoribonucleotide strands" "wherein the dsRNA is 15-21 nucleotides in length" is supported by the PCT priority application and hence the art cited is not available as prior art since it was published after the filing date of the present application.

Applicants would agree that the prior art rejections would be proper if the priority date for the claims is July 2, 2003 as asserted by the Examiner. Accordingly, Applicants arguments and the main issue to be decided on appeal are directed to the entitlement to priority claimed by Applicants.

The basis of Applicants claim to priority to PCT/DE00/00244 is that:

1) the priority document discloses and teaches isolated oligoribonucleotides consisting of two complementary oligoribonucleotide strands (dsRNA) that specifically inhibit the expression of a target gene where the dsRNA is 15-49 base pairs and where the two strands can be separate or linked;

2) the priority documents discloses and teaches a working Example using an isolated dsRNA that specifically inhibit the expression of a target gene where the dsRNA consist of two strands that are 21 nucleotides long where the two strands are linked

3) the amendment reciting the length range "15-21 nucleotides" and that the two strands are "separate non-linked" is supported by the specification, case law

and MPEP which allows the use of an internal value in a recited claim range to provide a new bound for the claim range

4) the presence of a linker in the working example cannot be viewed as requiring this feature to be added as a further limitations in claims reciting the new claim range

5) The statement by the Inventors at the end of the Example section that "even shorter dsRNA can be used for specifically inhibiting gene expression in mammals when the double strands are stabilized by chemically linking the single strands" is a conclusion about an experiment and not an admission or statement that "non-link" strands cannot work

6) Significant examples exist post filing, such as the cited Fosnaugh reference, that dsRNA of 15-21 nucleotides that is composed of separate, non-linked strands, can specifically inhibit the expression of a target gene in mammalian cells.

III. PCT/DE00/00244, US 09/889,802 And The Instant Application Disclose Isolated dsRNA Of 15-49 Base Pairs

The texts of PCT/DE00244, the US National Phase application US 09/889,802 and the instant divisional application are the same except for the filed claims.

These applications have written description support under 35 U.S.C. § 112 for isolated dsRNA that specifically inhibits the expression of a target gene wherein the dsRNA can be 15-49 base pairs. For example, at page 4, lines 1-8 of the application, it is stated that the dsRNA is "preferably 15 to 49 base pairs."

The Examiner does not seem to disagree with this position.

IV. The PCT Priority Document Discloses Isolated dsRNA Of 15-49 Base Pairs Composed Of Separate Strands And Linked Strands

The application discloses that the isolated dsRNA can be comprised of two separate strands which are synthesized separately. For example, at page 4, line 26 of the application, it is

disclosed that "the double-stranded structure is formed by two separate RNA strands or by autocomplementary regions. . . "

The application discloses that the dsRNA, composed of two separate strands, can have an additional chemical linker. For example, in the paragraph spanning pages 4 and 5 of the application, it is disclosed that "to inhibit dissociation in a particularly effective fashion, the cohesion of the complementary region II, which is caused by the nucleotide pairs, can be increased by at least one, preferably two, further chemical linkages."

The above, as well as the Examples, clearly provide written support for isolated dsRNA of 15-49 base pairs composed of two separate strands either with or without an additional chemical linkage.

The Examiner does not seem to disagree with this position.

V. The PCT Application Discloses An Example Within The Originally Cited Claim Range

Applicants provided several working examples of the claimed invention. In one Example, at page 17, lines 9-27 of the PCT application, Applicants synthesized two separate RNA stands of 21 nucleotides that contained an additional chemical linkage that were then hybridized to form a dsRNA of 21 nucleotides in length that was then further oxidized via aliphatic linkers and a disulfide bridge to form a dsRNA molecule made from two RNA strands that are 21 nucleotides long and which further contained a chemical linker between the two strands. This molecule was shown to be effective at specifically inhibiting the expression of a target gene in a mammalian cell.

Prior to the "further step of oxidation" Applicants were clearly in possession of an isolated oligoribonucleotide molecule consisting of two separate non-linked strands where the double stranded molecules was 21 nucleotides in length.

To illustrate one aspect of the invention, Applicants then created an isolated oligoribonucleotide molecule of 21 nucleotides in length where the two strands were linked together.

VI. Applicants Are Entitled To Use A Value Presented In An Example To Bound A New Claim Range

Based on MPEP 2163.05, and as supported by **In re Wertheim**, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976), Applicants used the working example of a dsRNA 21 nucleotides in length as a basis to amend the originally filed claims to provide a new upper bound of the length range disclosed in the application, namely the original length range of 15 to 49 was amended to claim the new range of 15 to 21 nucleotides. The Examiner rejected this amendment as new matter stating that the Example teaches isolated dsRNA made of strands 21 nucleotides in length with a linker and a linker needs to be present in any claim that relies on this Example as a basis for amendment.

Applicants disagree, particularly since it is now well established that dsRNA made of non-linked complementary strands of 15-21 nucleotides in length are effective at specifically inhibiting the expression of a target gene in a mammalian cells (for example see the cited Fosnaugh reference).

The presence of the chemical linkage in the 21 nucleotide long example does not eliminate from the scope of conception of the originally filed invention for "linked and non-linked dsRNA", it is simply an exemplification of a single embodiment. Applicants have used one of the features of this embodiment, strand length of 21 nucleotides, to provide support for a new claim range of 15-21 nucleotides. There is nothing in the Example that suggest that the only way the Applicants viewed that such agents could be made and used were as chemically linked molecules (as suggested by the Examiner) because it is clear that the inventors contemplated that additional chemical linkages was an optional element. The conclusion statement cited by the Examiner is simply a statement that the experiment worked: namely, shorter, linked oligoribonucleotides were effective at selectively inhibition the expression of a target gene in a mammalian cell.

Applicants assert that it is not required by case law precedence or PTO practice to limit the claims to recite all features found in a working example that is used to support a new claim range, namely the length limitation is distinct from and separate from the linkage limitation. The cited case of **In re Wertheim**, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976) and the patents that issued there from are directly on point.

In Wertheim, the court found that the Applicants were entitled to use 35% solids as a new lower bound in the originally claimed range of 25-60% solids because the use of 36% solids was disclosed in Example 2 (See Claim 2 in the Appendix of Wertheim, as well as US Patent No 4,565,706).

In addition to the limitation of solids, the application and claims had other limitations with respect to the invention, such as foam density, .1-.7 gm/cc (claim 3), add-back of stripped aromatic, .1-.5% (claim 13), ground particle sizes, .25-2 mm (claim 16), temperature, less than 100 degrees F (claim 4), layer thickness 10-40 mm (claim10), etc.

In Example 2, where the use of 36% solids was disclosed and formed the basis of a new bound for a claim range, several of the other limitations found in the method (and recited in dependent claims) were also exemplified in a scope less than that originally described in the application. Specifically, the working example that allowed Applicant to bound the claim range to 35% also had specific values for other range limitation, such as foam density of .6-.8 gm/cc, particle size, .1-.5mm and add back to extract of .6% by weight. However, none of these specific features that were used with the 36% solids example were required by the Court to be present in the claims to support the use of the exemplified % as a new bound in the claim range. The court clearly viewed these as distinct limitations. One limitation is of particular note, the amount of condensate that is added back in the Example is .6% while the application range is .1-.5%. Even this feature was not found to be required to be added to the claims to support the use of the exemplified 36% as a new bound for the claimed range.

In **In re Wertheim**, the Applicant used certain values for each of the limitations of the claimed method in order for it to be performed as a working example of the generically claimed method. As confirmed by the court's decision **In re Wertheim**, this did not constitute requirement that it was in any way necessary or required for the invention to function as claimed that each of these particular values be included as limitations in the claims. Similarly, in the present case, the Applicant choose one of the two embodiments, namely using linked from the genus of disclosed linked and non-linked dsRNA, in order to provide a working example of the generically claimed invention.

Using the present Examiner's logic, all claims based on Example 2 in Wertheim would need all of the other specific values for each of the other limitations that are disclosed in the application, and this was clearly not required by the court in the case.

In the present pending claims, the pertinent feature of length, 15-21 nucleotides, is distinct from and separate from the other disclosed limitation, such as linked versus non-linked. This is identical to the situation faced in Wertheim, using one feature of an example to support a new claim range while leaving other features that are present in the example out of the claims.

As stated in Wertheim "The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient" **In re Wertheim at page 265, column 1, see also In re Lukuch 442 F.2d 968.** The Examiner has not met this burden here and the case law precedent supports Applicant's position.

VII. The Prior Art Rejection Can Be Withdrawn Upon Granting Of Priority Date For The 15-21 Claim Range

The basis of the Examiners rejections is that the present claims are not supported by the priority documents and are only afforded a priority date of July 2, 2003. As such, the Examiner has cited Fosnaugh that was published after the priority applications, but before the date of the instant application as prior art, which anticipates the claims.

As discussed extensively above, the presently pending claims are supported by the PCT priority application and therefore the effective filing date for these claims is January 29, 2000.

The reference cited by the Examiner is not available as prior art since it was published after January 29, 2000.

Accordingly, the prior art rejection may be properly withdrawn.

CONCLUSION

For the reasons set forth above, Appellants respectfully request that the rejections of claims 4-9 be reversed.

(viii) Appendix of Claims

4. An isolated oligoribonucleotide consisting of two separate non-linked complementary oligoribonucleotide strands (dsRNA),

wherein the dsRNA is 15 to 21 nucleotides in length,

wherein the dsRNA does not comprise a full length RNA transcript of a mammalian target gene,

wherein one strand of the dsRNA is complementary to less than the full length of an RNA transcript of said mammalian target gene,

and wherein the oligoribonucleotide specifically inhibits the expression of said mammalian target gene.

5. The oligoribonucleotide of claim 4, wherein said dsRNA consists of a length of 21 nucleotides.

6. The oligoribonucleotide of claim 4, wherein the RNA transcript is a primary or a processed RNA.

7. The oligoribonucleotide of claim 4, wherein said oligoribonucleotide is modified so as to be resistant to RNA degradation.

8. The oligoribonucleotide of claim 4, wherein said one strand of said dsRNA is fully complementary to less than the full length of an RNA transcript of a mammalian target gene.

9. The oligoribonucleotide of claim 4 or 8, wherein said two separate complementary strands are fully complementary to each other.

(ix) Evidence Appendix

None

(x) Related Proceedings Appendix

None

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Attached is a Notice of Appeal and a Petition for Extension of Time for one month. Please apply the $500 fee for the Appeal Brief, the $500 fee for the Notice of Appeal, the $120 fee for the Petition for Extension of Time, and any other necessary charges or credits to Deposit Account No. 06 1050, referencing Attorney Docket No. 14174-104US5.

Respectfully submitted,

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